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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/578,485	06/05/2006	Peter Carmeliet	BJS-4465-10	7876
23117	7590	02/20/2009	EXAMINER	
NIXON & VANDERHYE, PC 901 NORTH GLEBE ROAD, 11TH FLOOR ARLINGTON, VA 22203			POPA, ILEANA	
ART UNIT	PAPER NUMBER			
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/578,485	CARMELIET, PETER	
	Examiner ILEANA POPA	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If no period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 22 December 2008.  
 2a) This action is FINAL.      2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 1 and 3-6 is/are pending in the application.  
 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 1 and 3-6 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) Notice of References Cited (PTO-892)  
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)  
 3) Information Disclosure Statement(s) (PTO/0256/06)  
 Paper No(s)/Mail Date \_\_\_\_\_

4) Interview Summary (PTO-413)  
 Paper No(s)/Mail Date \_\_\_\_\_  
 5) Notice of Informal Patent Application  
 6) Other: \_\_\_\_\_

**DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/22/2008 has been entered.

Claim 2 has been cancelled. Claim 1 has been amended.

Claims 1 and 3-6 are pending and under examination.

***Claim Rejections - 35 USC § 103***

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. Claims 1and 3-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beck et al. (Mechanism of Development, 1999, 88: 221-227, of record), in view of both Witte et al. (Microscopy Research and Technique, 2001, 55: 122-145, of record) and Bartel et al. (Anat Embryol, 2000, 202: 55-65, of record).

Beck et al. teach a transgenic *Xenopus* comprising GFP (i.e., a reporter gene) under the control of mammalian tissue specific promoters such as the pancreatic-

specific PDX-1 promoter, the liver-specific transthyretin promoter, and the small intestine-specific IFABP promoter, wherein the promoters drive specific GFP expression in pancreas, liver, and small intestine, respectively (claim 1) (Abstract, p. 221, column 2, p. 223, column 2, p 224, columns 1 and 2, p. 225, column 1). Beck et al. also teach a method of obtaining the transgenic *Xenopus* animals comprising GFP, wherein GFP expression is driven by the promoters above (claim 3) and a method of visualizing the pancreas, liver, and small intestine by observing GFP expression in these transgenic *Xenopus* animals (claim 5) (p. 225, column 2, last paragraph, p. 226, column 1, third full paragraph). Although Beck et al. teach that transgenic *Xenopus* animals comprising mammalian tissue-specific promoters driving GFP expression can be generally used to study later developmental stages, such as organogenesis (Abstract, p. 221, column 2, first full paragraph, p. 225, column 2, third full paragraph), they do not specifically teach making transgenic *Xenopus* comprising GFP under the control of promoters specific for expression within the lymphatic vessels (claims 1, 3, and 4) nor do they teach using this transgenic *Xenopus* to visualize the lymphatic vessel system (claim 5) or to screen for compounds capable of modulating lymphatic vessel development (claim 6). Witte et al. teach that the lymphatic vessel development is poorly understood and suggest the use of experimental models to elucidate the mechanism of lymphatic vessel development and to develop new therapies (claim 6) (Abstract, p. 124, column 1, p. 127, column 1, p. 138, column 1). It would have been obvious to one of skill in the art at the time the invention was made, to modify the transgenic *Xenopus* of Beck et al. by using promoters driving specific GFP expression in lymphatic vessels (it is noted that the prior

art teaches that *Xenopus* has lymphatic vessels, see Bartel et al., p. 59, Fig. 4) and use the resulting transgenic animals to study the development of lymphatic vessel system and to screen for agents which can modulate lymphatic vessel development as taught by Witte et al., with a reasonable expectation of success. The motivation to use transgenic *Xenopus* and not the transgenic mice of Witte et al. is provided by Beck et al., who teach that compared to mice, *Xenopus* offers many advantages such as large number of transgenic animals in one day and visualization of GFP activity in live embryos at stages that are not accessible to mammals (p. 225, column 2, second full paragraph). The motivation to use the transgenic *Xenopus* in a method of screening is provided by Witte et al., who teach the necessity to identify agents able to modulate lymphatic vessel growth (p. 138, column 1). It is noted that, by doing so, one of skill in the art would also practice a method of visualization of the lymphatic vessel system (claim 5). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that transgenic *Xenopus* expressing GFP or transgenes in desired tissues/organs can be successfully made and used. With respect to the limitation of comparing the effect of the tested agent by comparing treated and untreated animals (claim 6), it is noted that such a step is inherent to any method of screening for modulating agents. With respect to the limitation of the lymphatic vessel system comprising lymphatic vessels, sacs and a lymphatic heart (claim 1), such is inherent to the *Xenopus* lymphatic system. It is also noted that Witte et al. teach that the tadpoles have a lymph heart (p. 122, column 1). With respect to the limitation of the promoters recited in claim 4, Witte et al. teach that

VEGFR-3 and Prox-1 are specifically expressed in the lymphatic vessels (p.124).

Therefore, one of skill in the art would have known to use one of these promoters to specifically express GFP in the lymphatic vessels of *Xenopus*. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that Beck does not specifically teach making transgenic *Xenopus* comprising GFP under the control of promoters specific for expression within the lymphatic system, wherein such transgenic *Xenopus* are useful for the visualization of the lymphatic vessel system and for screening assays. Applicant argues that Beck et al. are silent about a model of the lymphatic system and only describe a method of visualizing the pancreas, liver and small intestine. With respect to Witte et al., Applicant argues that the reference, which is a state of the art review article published two years after Beck, appears to suggest that sufficient animal models are available and provides no motivation to use *Xenopus* as a model in place of the existent mammalian models. With respect to Bartel et al., Applicant argues that the reference relates to the microvasculature of the lung in tadpoles and does not cure the deficiencies noted above with regard to Witte et al and Beck. Applicant submits that the cited art fails to provide motivation for one of ordinary skill to have made the claimed invention. One of ordinary skill in the art would not have reasonably predicted or considered that a tadpole could be used as a model for the human lymphatic system and for studying lymphangiogenic candidates. Prior to the present invention, one of ordinary skill would not have reasonably predicted that tadpoles possessed a functional lymphatic vessel system, as

required by the present claims. Moreover, one of ordinary skill in the art would not have reasonably predicted that it would have been possible to visualize a system comprising lymphatic vessels, lymphatic sacs and lymphatic hearts, as required by the present claims. For these reasons, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged however, they are not found persuasive for the following reasons:

Applicant argues that Beck et al. are silent about a model of the lymphatic system, that Witte et al. do not provide the motivation to combine, and that Bartel et al. relates to the microvasculature of the lung in tadpoles and does not cure the deficiencies noted above with regard to Witte et al. and Beck. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is the combination of references which teaches the claimed invention. The Examiner clearly indicated that the motivation to combine is provided by both Beck et al. and Witte et al., and not by Witte et al. alone, as Applicant argues (see above). Witte et al. teach using mammalian models to screen for agents capable of modulating lymphatic vessel growth. By teaching that *Xenopus* offers many advantages over the mammalian models, Beck et al. provides the motivation to use transgenic *Xenopus* tadpoles instead of mammalian models. In addition, because Bartel et al. and Witte et al. teach the existence of lymphatic vessels and lymph heart in *Xenopus* tadpoles, one of ordinary skill in the art would have

reasonably predicted that it would have been possible to visualize a system comprising lymphatic vessels and lymph heart. With respect to the lymphatic sacs, such is inherent to the tadpole lymphatic system. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention. The discovery of a previously unappreciated property of a prior art composition does not render the old composition patentably new to the discoverer" (2112 [R-3]). For these reasons, the rejection is maintained.

4. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/  
Examiner, Art Unit 1633